

Enantioselective Synthesis of Bicyclo[1.1.0]butanes

Research Topic Seminar

Yongzhao Yan

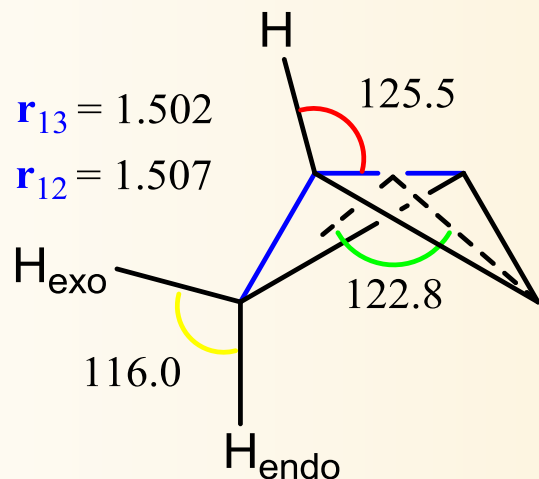
Aug 27 2011

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Background

- Structure determined using **NMR***, **electron diffraction***, **microwave spectroscopy**** and accompanied by extensive theoretical calculations***.
- Bond length slightly shorter than cyclopropane (**1.512 Å**)*
- **Central** bond and **lateral** bond have similar length.*
- Substituents on **C1** and **C3** are restricted to one hemisphere.



Structural parameters by electron diffraction method. Angles are given in degrees and bond lengths in Ångstroms.

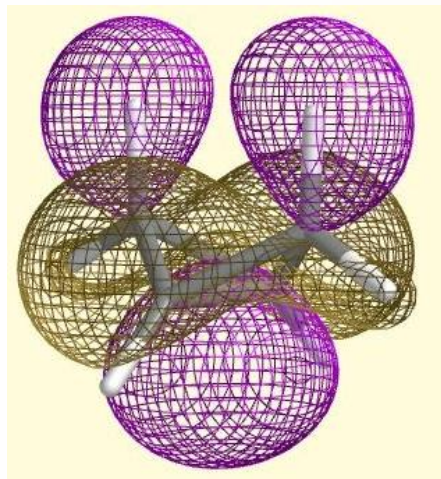
*Meiboom, S.; Snyder, L. C., *Acc. Chem. Res.* **1971**, 4, 81.

Cox, K. W. H., M. D.; Nelson, G.; Wiberg, K. B., *J. Chem. Phys.* **1969, 50, 1976.

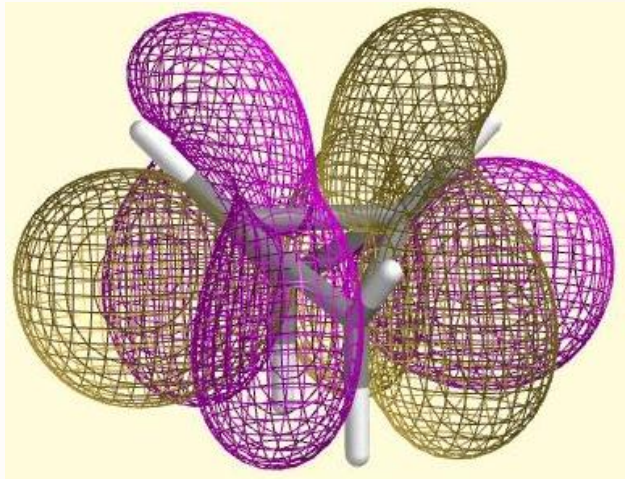
***Gassman, P. G.; Greenlee, M. L.; Dixon, D. A.; Richtsmeier, S.; Gougoutas, J. Z., *J. Am. Chem. Soc.* **1983**, 105, 5865.

Frontier Orbital of Bicyclobutanes

- **LUMO** and **HOMO** are all associated with central bonds.*

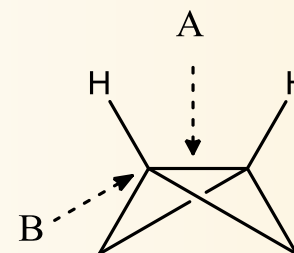


HOMO (-0.245 a.u.)



LUMO (0.107 a.u.)

- Two different ways of protonation approach, A and B. The stabilization energy is greater for path B than path A by **33 kcal/mol*****



*Wiberg, K. B.; Ellison, G. B.; Peters, K.S., *J. Am. Chem. Soc.* **1977**, 99, 3942.

**Calculated by Spartan 08 using density functional B3LYP 6-31G* in vacuum.

***Wiberg, K. B.; Ellison, G. B.; Peters, K.S., *J. Am. Chem. Soc., Chem. Commun.* **1973**, 29, 747.

The Nature of the Central Bond

- *Ab initio* calculations show that **96%** *p* character of central bond. (cyclopropane, **86%**)*
- $^1J_{\text{CH}}$ for $\text{C}_1\text{-H}_1$ corresponds to **40%** *s* character of the C-H bond hybrid.
- $^1J_{\text{CC}}$ values for $\text{C}_1\text{-C}_3$ are exceptionally low; using some approximations, Pomerantz calculated around **89%** of *p* character of the central bond.**
- Hückel calculations assign *p* character to the central bond (*p*- σ and *p*- π ratio was estimated to **5:1*****)

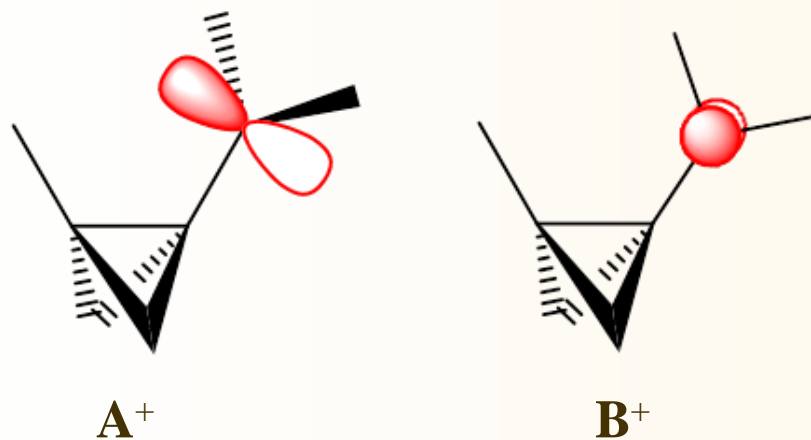
*Newton, M. D.; Schulman, J.M., *J. Am. Chem. Soc.* **1972**, *94*, 767-773.

Pomerantz, M.; Hillenbrand, D., *J. Am. Chem. Soc.* **1973, *95*, 5809-5810

***Schulman, J. M.; Fisanick, G. J., *J. Am. Chem. Soc.* **1970**, *92*, 6653.

Π Character of the Central Bond

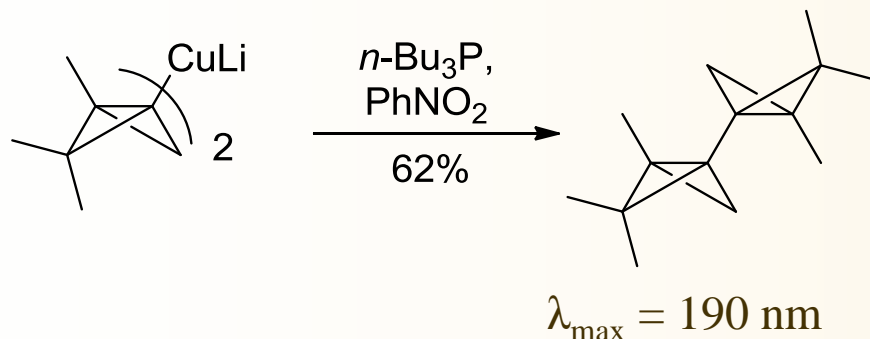
- Ab initio* calculations show that \mathbf{A}^+ conformer is **32 kcal/mol** more stable than \mathbf{B}^+ .*



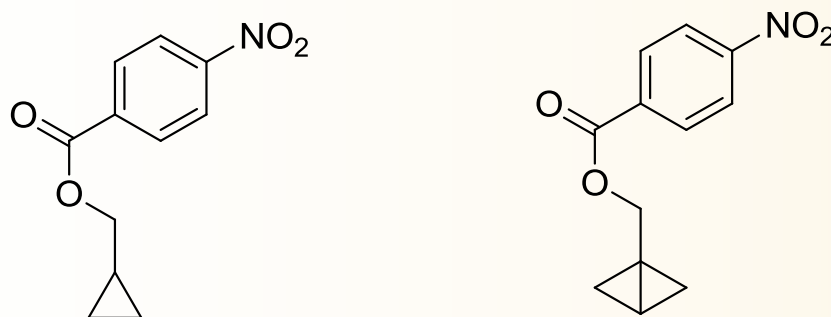
*Greenberg, A., *Tetrahedron Lett.* **1978**, 19, 3509.

Π Character of the Central Bond

- Bicyclobutane dimer shows **red shift** in UV/VIS spectrum.*



- Solvolysis of bicyclobutane is **1000 times** faster than cyclopropyl derivative.**







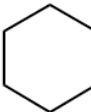
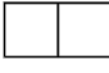


*Moore, W. R.; Costin, C. R., *J. Am. Chem. Soc.* **1971**, *93*, 4910.

Wiberg, K. B.; Lampman, G. M.; Ciula, R. P.; Connor, D. S.; Schertler, P.; Lavanish, J., *Tetrahedron* **1965, *21*, 2749.

Strain Energy of Bicyclobutanes

- Large strain energy (**66 kcal/mol**)*
- The strain energy in bicyclo[1.1.0]butane does not follow the additive rule for small bicyclic systems.
- **1,3 carbon/carbon** interaction**
- **Baeyer strain*****

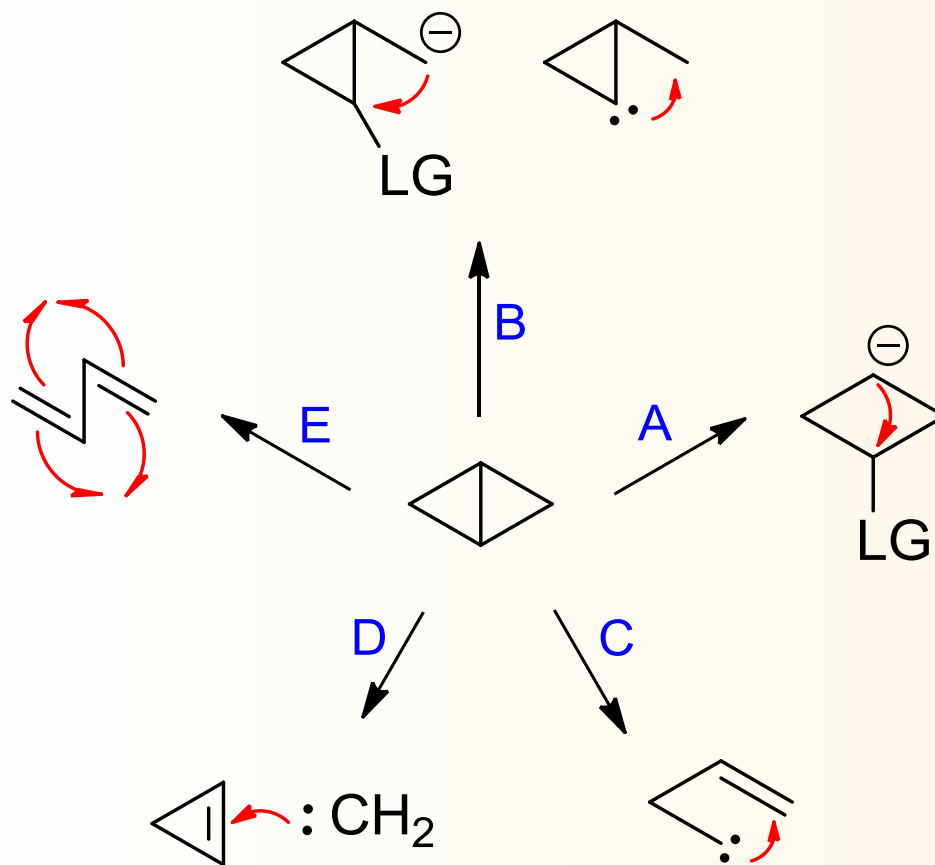
 6	27.5	 1	66
 7	26.5	 10	56
 8	1.8	 11	26
 9	0.5	 12	36

*Wiberg, K.B., *Angew. Chem. Int. Ed.* **1986**, *25*, 312-322.

Bauld, N. L.; Cessac, J.; Holloway, R. L., *J. Am. Chem. Soc.* **1977, *99*, 8140.

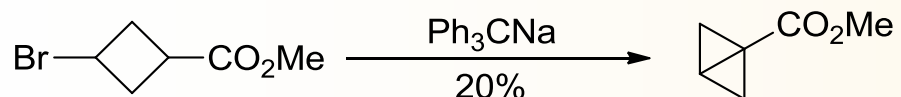
*** Baric, D.; Maksic, Z. B., *Theor. Chem. Acc.* **2005**, *114*, 222.

Synthesis of Bicyclobutane

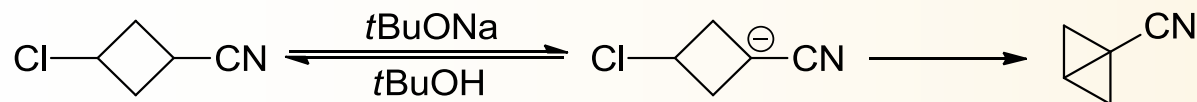


A: Synthesis of Central Bond

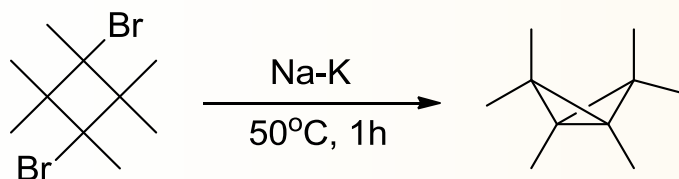
- Wiberg and Ciula reported using sodium triphenylmethide to furnish bicyclobutanyl methylcarbonxylate in 20% yield. (**1st synthesis**)*



- The reversibly formed anion possesses a low barrier of inversion, and it was demonstrated that the subsequent displacement step is **stereospecific**.**



- The central bond can also be joined by **Wurtz-type** protocol.***



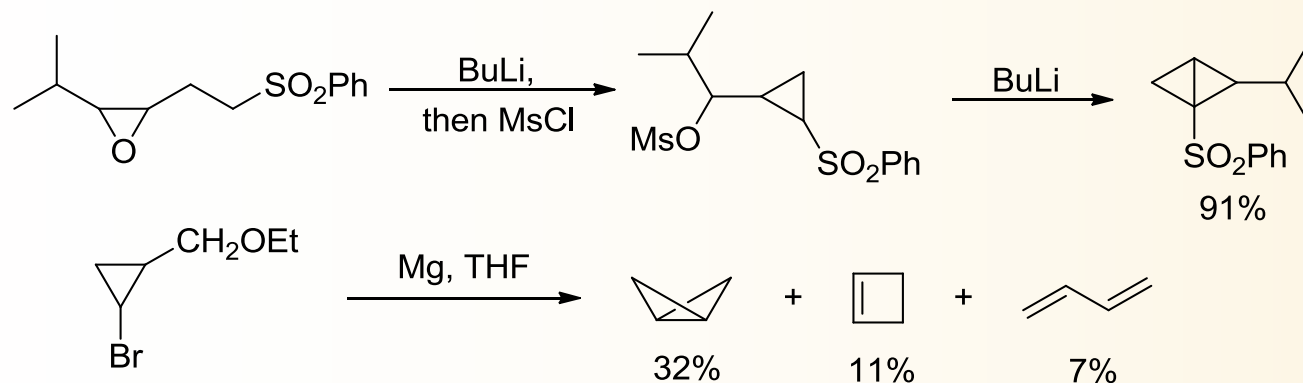
*Wiberg, K. B.; Ciula, R. P., *J. Am. Chem. Soc.* **1959**, *81*, 5261.

Hoz, S.; Aurbach, J. *Am. Chem. Soc.* **1980, *102*, 2340.

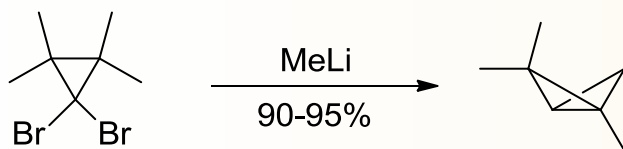
***Hamon, D. P. G., *J. Am. Chem. Soc.* **1968**, *90*, 4475.

B: Synthesis of Lateral Bond

- From properly functionalized cyclopropanes, bicyclobutane could be accessed *via* intramolecular displacement of a leaving group.*,**



- The most common approach for construction of this bond involves insertion of cyclopylidene into a CH bond.***



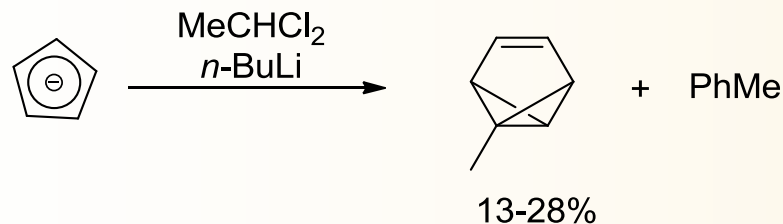
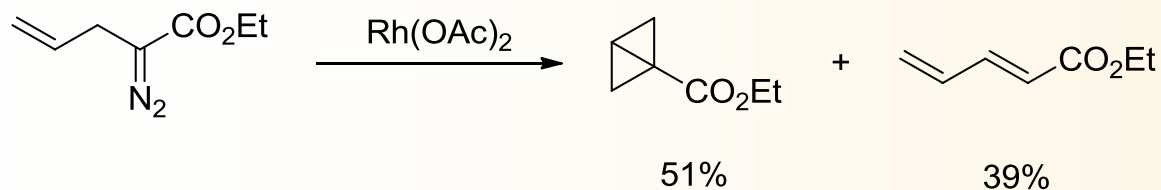
*Weber, J.; Haslinger, U.; Brinker, U. H., *J. Org. Chem.* **1999**, *64*, 6085.

Abramova, N. M.; Zotova, S. V., *Izv. Akad. Nauk.* **1979, 697.

***Brown, D. W.; Hendrick, M. E.; Browne, A. R., *Tetrahedron Lett.* **1973**, 3951.

C: Intramolecular Carbene Insertion

- The simultaneous formation of the central and lateral bonds is performed by **intramolecular carbene insertion** of a carbene into an alkene.**,**

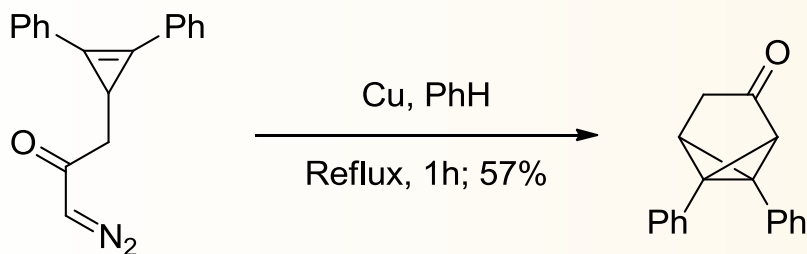


*Ikono, N.; Takamura, N.; Young, S. D.; Ganem, B., *Tetrahedron Lett.* **1981**, 22, 4163.

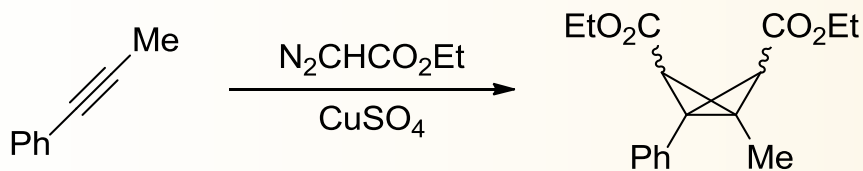
Christl, M.; Kemmer, P.; Mattauch, B., *Chem. Ber.* **1986, 119, 960.

D: Carbene Addition to Cyclopropene

- Some highly strained systems have also been prepared by decomposition of diazo compounds.*



- But this type reaction is usually not stereospecific and the product is a mixture of *endo*- and *exo*-isomers.**

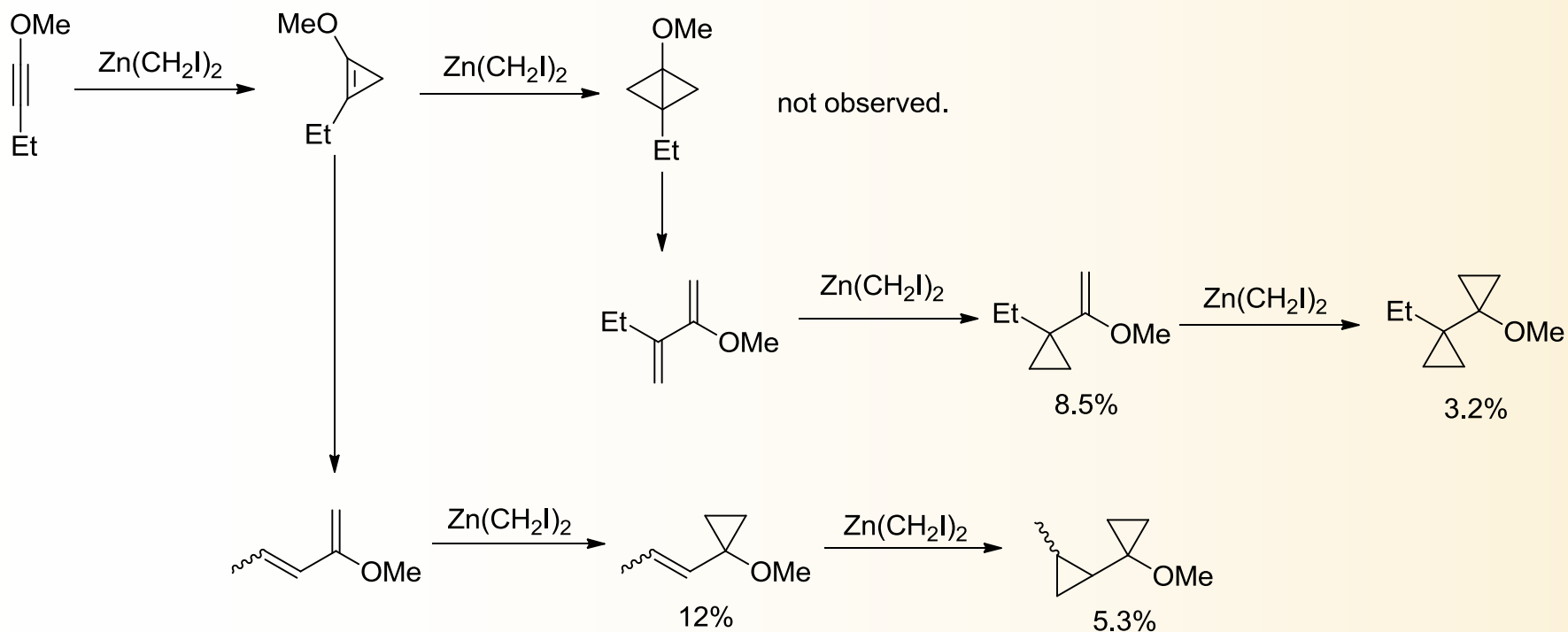


*Masamune, S., *J. Am. Chem. Soc.* **1964**, *86*, 735.

Small, A., *J. Am. Chem. Soc.* **1964, *86*, 2091.

Zinc Carbenoids - Reaction with Alkyne

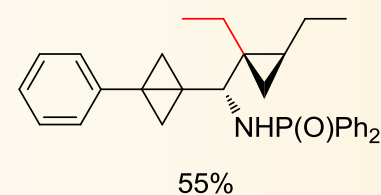
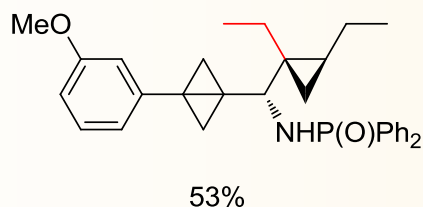
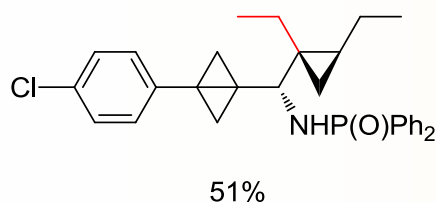
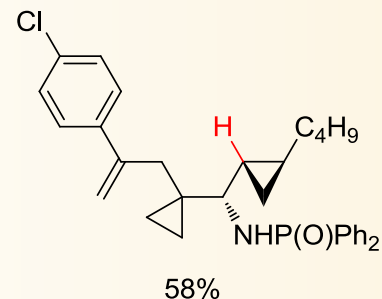
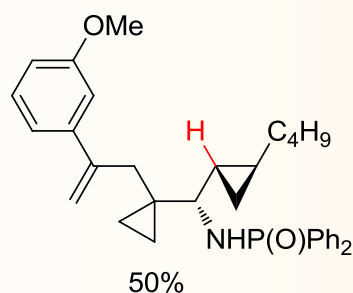
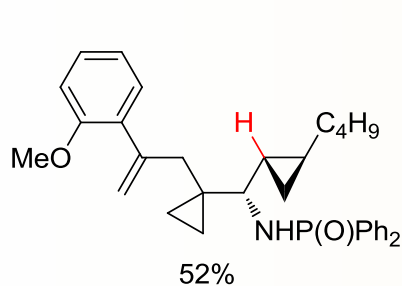
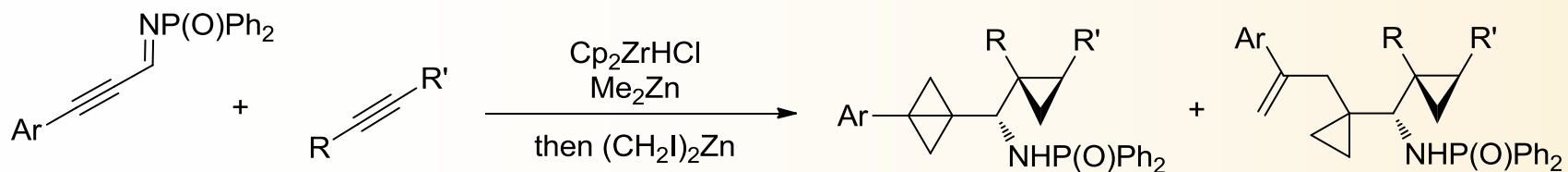
- Zinc carbenoid generated from metallic zinc and CH_2I_2 were shown to react with alkyne to give mixture of cyclopropanated products.*



*Jautelat, M.; Schwarz, V., *Tetrahedron Lett.* **1966**, 5101.

Cascade Synthesis of Bicyclobutanes

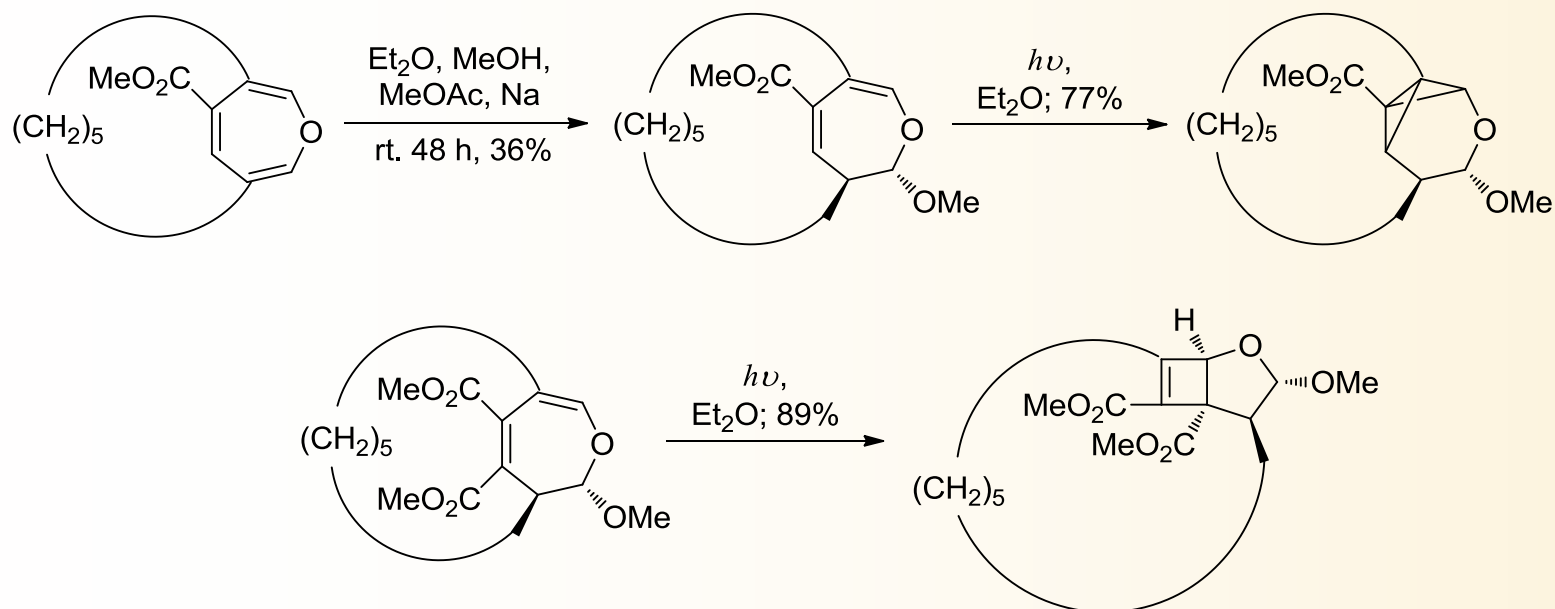
- CH₂ unit could be delivered to propargyl amine to give bicyclobutanes or dicyclopropylmethylamine in good yield.



*Wipf, P.; Stephenson, C. R. J.; Okumura, K., *J. Am. Chem. Soc.* **2003**, *125*, 14694.

E: Photochemical Activation of Diene

- The last method for the synthesis of bicyclobutane involves the **simultaneous formation** of two lateral bonds.**,**



*Tochterman, W.; Popp, B.; Mattauch, A.-K.; Peters, E.-M.; Peters, K.; von Schnering, H. G., *Chem. Ber.* **1993**, 126, 2547.

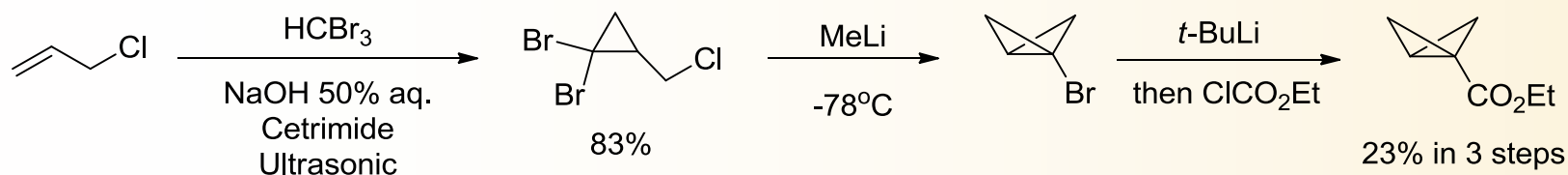
Tochterman, W.; Panitzsch, T.; Peschanel, M.; Wolff, C.; Peters, E.-M.; Peters, K.; von Schnering, H. G., *Lieb. Ann.* **1997, 1125.

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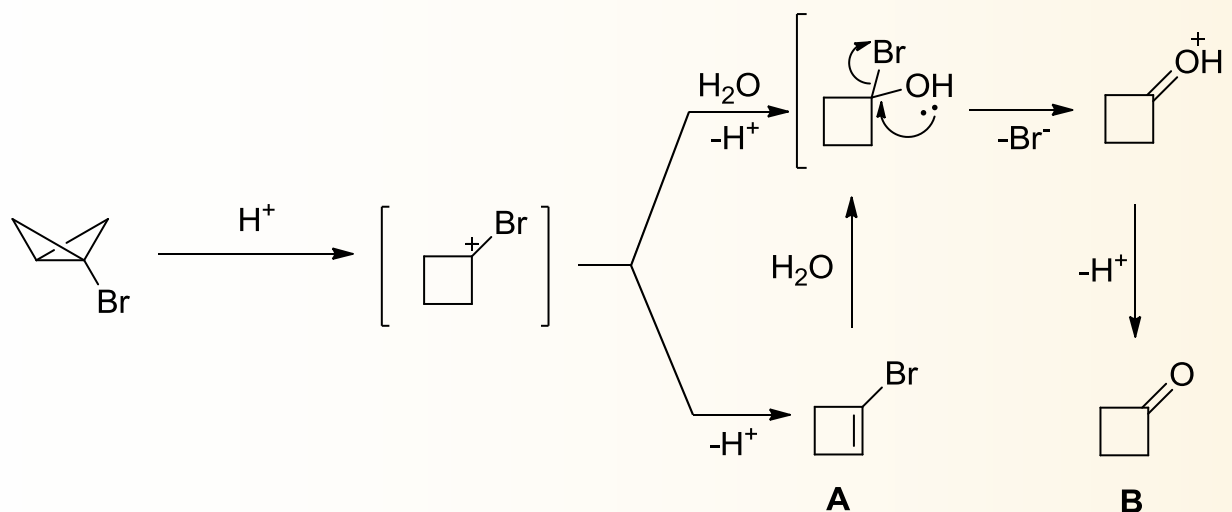
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6. Summary

Synthesis by Addition of Bicyclobutyl Lithium Reagents

- This method is one of the most **effective** methods in the synthesis of bicyclobutane.*



- It was used as an alternative route to synthesize **cyclobutanone B** (23%).**

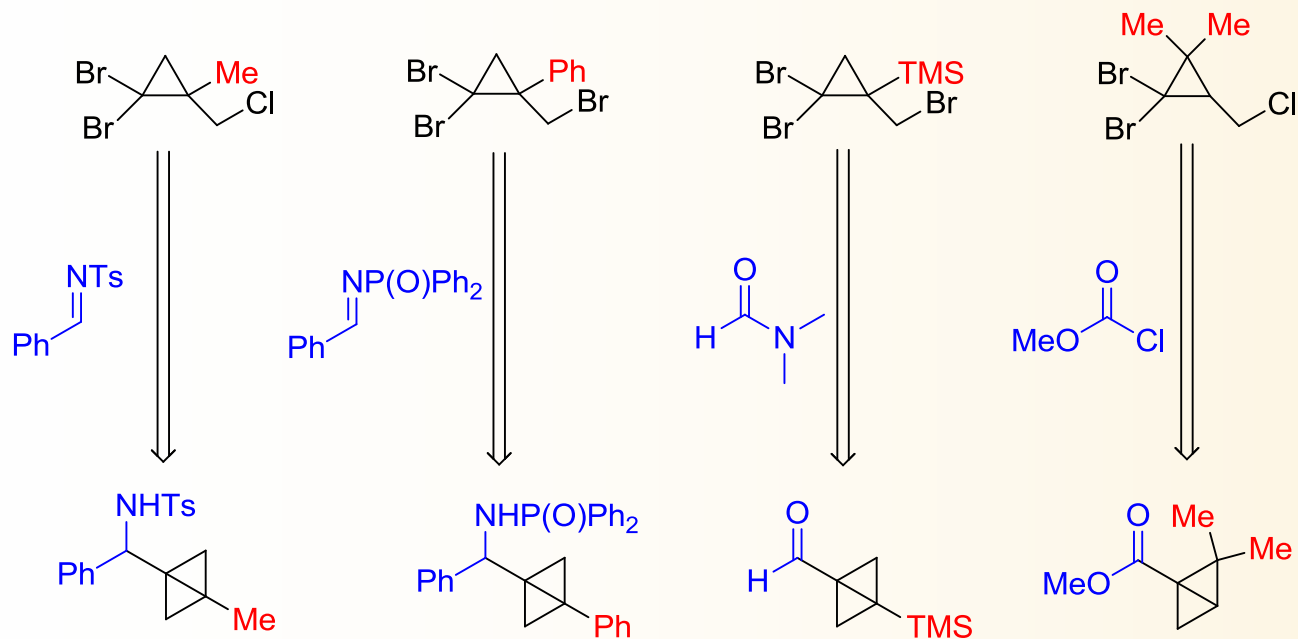


*A. Duker, G. Szeimies, *Tetrahedron Lett.* **1985**, 26, 3555-3558;

J. Weber, U. Haslinger, U. H. Brinker, *J. Org. Chem.* **1999, 64, 6084 – 6086.
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Synthesis by Addition of Bicyclobutyl Lithium Reagents

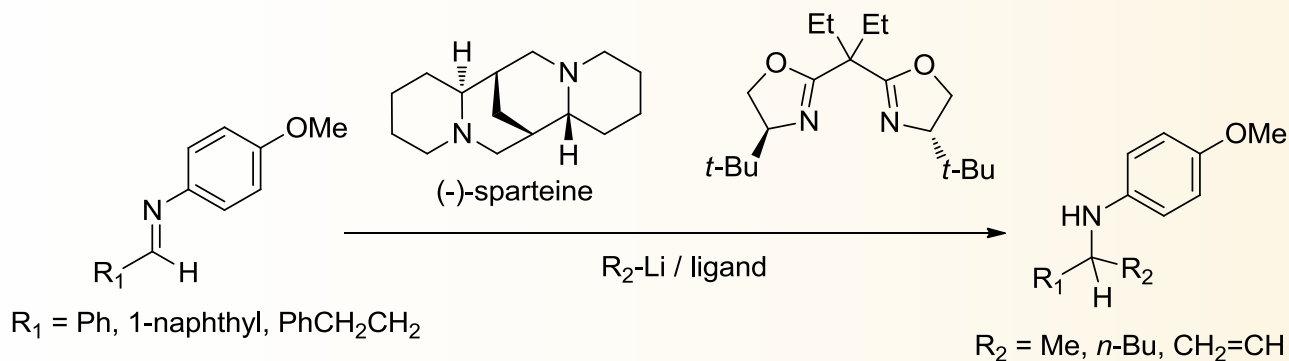
- This method is further expanded by our group with different *gem*-dibromocyclopropane and carbonyl electrophiles.*



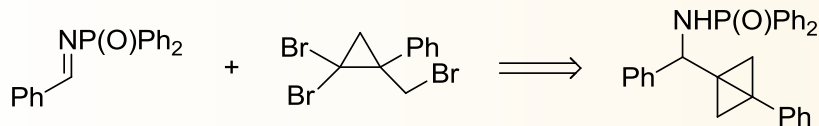
*Walczak, M. A. A. Ph.D. dissertation. University of Pittsburgh. 2009

Enantioselective Addition of Bicyclobutyl Lithium Reagents

- Many methodologies for the enantioselective addition of lithium reagents rely on the **electron-rich** imine with catalytic amount of chiral imine.*



- Due to the **bulky** and **unstable** nature of bicyclobutyllithium reagent, we expect the **electron-poor** imine (*P, P*-diphenylphosphinyl imine) may serve as suitable precursors for the addition.



*Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C., *J. Am. Chem. Soc.* **1994**, *116*, 8797.

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